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SURFACE CONDITIONING OF CARDIOVASCULAR 316L STAINLESS STEEL STENTS: A REVIEW

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Cardiovascular disease is the leading cause of death worldwide and 90% of coronary interventions consists in stenting procedures. Most of the implanted stents are made of AISI 316L stainless steel (SS). Excellent mechanical properties, biocompatibility, corrosion resistance, workability and statistically demonstrated medical efficiency are the reasons for the preference of 316L SS over any other material for stent manufacture. However, patients receiving 316L SS bare stents are reported with 15–20% of restenosis probability. The decrease of the restenosis probability is the driving force for a number of strategies for surface conditioning of 316L SS stents. This review reports the latest advances in coating, passivation and the generation of controlled topographies as strategies for increasing the corrosion resistance and reducing the ion release and restenosis probability on 316L SS stents. Undoubtedly, the future of technique is related to the elimination of interfaces with abrupt change of properties, the elimination of molecules and any other phase somehow linked to the metal substrate. And leaving the physical, chemical and topographical smart modification of the outer part of the 316L SS stent for enhancing the biocompatiblization with endothelial tissues.

Keywords: Medical materials; biomaterials; implants.

1. Relevance of Cardiovascular Disease

Cardiovascular disease is the leading cause of death worldwide. Cardiovascular diseases were responsible for 17.5 million deaths in 2012. 7.4 million and 6.7 million people died of ischaemic heart disease and stroke, respectively.[1] Ischaemic heart disease and stroke are diseases characterized by reduced or interrupted blood supply to the heart and the brain, respectively. 90% of coronary interventions consist in stenting procedures in order to restore blood flow.[2] In addition, carotid artery stenting is the preferred technique after carotid endarterectomy in patients at stroke risk.[3]

The global market for artery disease treatment devices is expected to increase from 14,000 million USD per year in 2015 to 24,000 million per year in 2021. In particular, the stent market will increase from 9,000 million USD per year to 16,000 million USD per year in the same period.[4]

2. Clinical Limitations of Stenting Procedures

Despite the significant improvement of stenting procedures over regular percutaneous transluminal coronary angioplasty, it presents some serious clinical limitations that include intra stent restenosis and thrombosis.[5–7] As most cardiovascular stents are made of metallic alloys, corrosion plays an important role on the implant outcome.[8–10] The corrosion process releases toxic ions into the surrounding tissues and into the blood flow changing the chemistry at the implant zone by promoting an overgrowth of endothelial cells, the adhesion and activation of immune cells and promoting an inflammatory response and restenosis.[11] Corrosion also affects the mechanical properties and the integrity of the implant. Stent fracture due to corrosion attack has been detected in 1–3% of coronary cases and this figure increases to 37% in femoropopliteal stenting.[12]

3. Technical Solutions to Metal Ion Release

Significant efforts have been made to reduce the release of harmful ions from implanted stents to the endothelium and blood flow. The development of geometries, materials and surfaces with high corrosion resistance while keeping good mechanical, biological and manufacture properties is required.

Metals are the preferred material for stent manufacture. The most common alloys used for stent manufacture are 316L stainless steel (SS), cobalt–chromium, nickel–titanium and platinum–iridium alloys, and tantalum, titanium, iron and magnesium pure metals. A detailed description of the advantages and disadvantages of each cited material can be found in the literature.[13]

316L SS is a ferrous alloy with 10–14, 16–18 and 2–3 weight percent of nickel, chromium and molybdenum, respectively.[14] 316L SS is the material most commonly used for stent manufacture. The reasons for this preference are its excellent mechanical and corrosion resistance properties.[15,16] 316L SS naturally develops a corrosion resistance oxide layer on its surface. This layer is believed to be mainly composed of chromium oxide, small parts of iron and nickel oxides and traces of their elemental forms. The full comprehension of the chemical and physical properties and the mechanism of formation of this layer are cutting edge topics of investigation.[17,18] However, when subjected to extremely corrosive environments, such as blood and chloride solutions, the heterogeneous oxide layer is attacked and chemical reduction occurs.[19–21]

316L SS may be responsible for allergic reactions when implanted.[22–24] The release of metals constituting the 316L SS alloy may induce local immune response and inflammatory reactions. And these are proposed to be responsible for intimal hyperplasia and in-stent restenosis.[9,25–27] Moreover, 316L SS is incompatible with magnetic resonance imaging techniques and its fluoroscopic visibility is very low.[28,29]

3.1. *Nickel-reduced SS alloys*

A reduction of the allergic response have been tried by decreasing the amount of nickel in the SS. A variety of SS grades with modified alloy concentrations has been tested with no clear advantages. The decrease of the nickel content in the SS alloy effectively decreases the allergic response of tissues in contact with the SS. But, in turn, it destabilizes the non-magnetic state and decreases the corrosion resistance of the resulting alloy.[30–32] Up to now, the use of alternative SS has never compromised the great supremacy of 316L SS for stent manufacture.

The fundamentals of the allergic response of endothelial tissues to nickel alloys contact remains incompletely understood. The first statistical association between nickel allergy and stent restenosis was reported in the year 2000.[33(32a)] This study was made on the diagnosis of 131 patients. Patients with nickel allergic response to patch-tests were reported with higher probability to suffer stent restenosis than patients without adverse responses to nickel patch-tests. This tendency was confirmed by several independent studies.[34,35] In addition, a recent report proposed the nickel allergy response as an important factor for stent thrombosis.[36] Conversely, other studies based on the observation of clinical records of 34,[37] 43,[38] 18,794,[39] 50,[40] and 29[41] patients concluded that there is no statistical evidence to ensure that metal allergy plays a role in the restenosis process.

Afterwards, the collection of statistical evidence and the efforts to understand the physiology of the nickel allergy response of endothelial tissues in stenting procedures were interrupted by the fast and successful introduction of drug eluting stents. The local

release of quimio drugs at the implantation site was pretended to inhibit the restenosis processes independently of its cause. However, restenosis continue occurring in a significant proportion of stenting procedures.[34] And, the scientific community regained interest in the comprehension of the nickel allergy response.[42]

3.2. *Optimization of geometrical design*

Great efforts have been carried out in the geometrical design of the stent's struts and cells in order to homogeneously distribute plastic deformation and residual tension during and after the expansion process of the stent.[43–45]

Homogeneous distribution of strain and stress in the metal substrate minimize the surface chemical potential gradients through the stent piece.[46] Then, the chemical potential difference between the stent and the surrounding medium is also minimized, which in turn is evidenced as a decrease of the corrosion susceptibility of the material.[47–50]

Geometrical design efforts are also oriented to avoid fracture of struts and cells and to allow expansion and contraction according to the beats of the restored blood vessels. The absence of fracture is of great importance to warrant the mechanical functionality of the stent. The reasons for stent fracture are not yet fully understood. However, strong evidence relates stent fracture with mechanical fatigue of the stent material as consequence of heart beating and corrosive physiological environment.[51,52] The mechanical fatigue of the stent material is intimately related to its microstructure. The dimensions stent struts are similar to crystal dimensions of the 316L SS polycrystalline alloy. Several works deal with computational struts design in relation with 316L SS microstructure in an attempt to minimize fatigue and fracture processes.[53–56]

Endothelial tissues constantly experience expansion and contraction pulses according to the beat frequency of the circulatory system. Some researchers proposed that restenosis may be the response of immobilized endothelial tissues due to implantation of rigid stents. Therefore, new geometries and materials are now designed to allow the beating expansion and contraction in restored arteries.[57]

Finally, one of the latest approach in geometrical stent design is the development of inductive stents. Inductive stents are designed for non-invasive, externally controlled and local heating of endothelial tissues around the stent. The controlled heating of endothelial tissues may serve to minimize or avoid restenosis through hyperthermia phenomena.[58] Heat is transmitted from the metallic stent material to the endothelial tissues. The antenna geometrically designed stent is heated up by inductive energy absorption of externally applied electromagnetic microwaves.[59,60]

3.3. *Optimization of surface smoothness*

The surface smoothness determines the area of the stent in contact with the endothelium and plays an important role on the amount of protein adherence.[61,62] The higher is the smoothness of the stent surface, the lower is the activation and aggregation of platelets. Activation and further aggregation of platelets are recognized as the starting stage of thrombus formation.[63,64] In general, very smooth surfaces obtained by electropolish process enhance the resistance to pitting type corrosion of 316L SS in contact with human blood.[8,65,66] Additionally, the material resistance to static and fatigue loadings are also increased as a consequence of electropolish processes.[67]

Despite these advantages, a general theory which is able to explain the great diversity of electropolish results is still pending.[68] The situation have even increased in complexity by the recent development of a variety of electropolishing processes assisted by magnetic fields, ultrasound, pulsed currents and high density currents. Special attention must be addressed to high-current-density electropolishing and magneto-electropolishing processes due to its singular characteristics and great potential adaptation to 316L SS stent manufacture. High-current-density electropolishing can influence the chemical composition of the passive layer naturally occurring on the 316L SS surface after the electropolishing treatment while keeping all other advantages related to surface smoothness.[69,70] Magneto-electropolishing could be used to increase the amount of Cr^{+3}-based compounds and decrease the concentration of carcinogenic compounds of Cr^{+6} and nickel on the 316L SS stent surface.[71,72] Interestingly, magneto-electropolish treatment was also reported to increase the corrosion resistance to chloride ions, haemocompatibility, smoothness, surface removal of hydrogen and

free-metal atoms, fatigue resistance,[73,74] hydrophilicity,[75] and pitting corrosion[76] of 316L SS. Those results are explained by the induced increment of the Cr/Fe ratio, the increment of the amount of Cr and Fe oxides and hydroxides and the selective removal of magnetic Fe and Ni atoms from the non-magnetic austenite phase of 316L SS.[77–80]

However, the optimization of geometry and surface smoothness is not enough to avoid corrosion. Ultimately, patients receiving 316L SS bare stents with uniform strain–stress distribution along struts are reported with 15–20% of restenosis probability.[81]

4. Surface Coatings On 316L SS Stents

A number of materials and techniques were tried to coat 316L SS stents. These materials are intended to improve the biocompatibility of 316L SS. The coats are designed to impair the release of metal ions while keeping intact the excellent bulk mechanical properties of 316L SS stents. 316L SS coatings can be classified as inorganic coatings, polymeric coatings, organic-inorganic hybrid materials, porous materials and biological coatings.

4.1. *Inorganic coatings*

Inorganic coatings include gold, iridium oxide, silicon-based materials, titanium oxide and carbon. Gold is characterized for having higher corrosion resistance in atmospheric environment and higher radiopacity than 316L SS. However, clinical trials carried out using gold-coated stents resulted very unsatisfactory with 83% of restenosis probability.[82] The results were explained by the 100 times lower corrosion resistance, the higher electronegative surface and rougher surface of gold-coated stents in the intravascular environment when compared against uncoated 316L SS stents.[64,83,84]

Iridium oxide (IrO_2) is a nano-structured ceramic material used for coating application and had proven to exhibit higher corrosion resistance than 316L SS.[85] In addition, it has the capability to promote the decomposition of hydrogen peroxide (H_2O_2) in to H_2O and O_2 may decrease the inflammatory reaction and accelerate the endothelization of the stent.[86,87] H_2O_2 is very oxidizing molecule and it is produced at the metal surface when corroded. H_2O_2 may damage the endothelial tissue generating inflammatory reactions.[88] A randomized study of IrO_2-coated stents reported a 13.8% of restenosis during the first eight months after implantation.[89,90] These results are not far from those obtained from nude 316L SS. Such little improvement does not compensate the risk for cracking due to the low thoughtless and low adherence to the 316L SS substrate of the IrO_2 coating. Further evaluation is needed to warrant the efficacy and safety. Moreover, the catalytic mechanism of IrO_2 in the decomposition of H_2O_2 and its effect on thrombosis and restenosis responses are to be elucidated. Combined iridium and titanium oxide coatings have been tried. Advantages related to higher radiopacity and biocompatibility were observed.[91,92] However, conclusive clinical studies could not be found in the literature. Titanium oxide seems to be a flexible coating material. Multilayered coatings demonstrated its potential to combine desired properties. 316L SS stents were coated with a titanium oxide layer followed by a silane layer and finally a glycosylated layer in an attempt to develop a coat with improved corrosion and biocompatible properties and with the capability to immobilize antibody fragments.[93] Titanium oxide was also deposited over 316L SS stents and used as anchoring substrate of selenocystamine. Selenocystamine is a catalyst for nitric oxide production.[94] Nitric oxide is a strong vascular dilator tone that regulates the local cell growth and plays an important role in the physiology of endothelial tissues.[95]

Silicon-carbide is a semiconductor material with well-known antitrombogenic properties with promising advantages for stent coating. The high critical electron gap of this semiconductor coat lowers the electron transfer out of the stent material. This phenomenon is believed to be responsible for the decrease of the platelet and fibrin activation observed in physiological media.[96] The surface of SiC-coated tantalum stents showed lower platelet and leukocyte adhesion than the nude surface of 316L SS stents when tested under *in-vitro* circulation conditions.[97] In addition, SiCOH-coated 316L SS stents presented better endothelialization and anticoagulation properties compared against nude 316L SS stents when implanted in rabbits.[98] Silicon diamond-like carbon coatings presented good anticorrosion properties in simulated body fluids.[99] However, the clinical trials demonstrated that SiC-coated stents have almost the

same efficacy as bare 316L SS stents.[100] Further evaluation is required to elucidate the contradicted outcomes of the clinical trials.

Recently, silica deposited over 316L SS stents using sol–gel technique showed good corrosion and biocompatibility properties.[101] However, the technique is still far from clinical trials.

Pyrolytic carbon is a chemically inert material used for stent coating. This material has gained its recognition as safe and effective in long-term clinical records of implanted heart valves. The pre-clinical trials of nitinol carbon-coated stent conducted in pigs, showed good endothelialization, absence of thrombotic processes and low inflammatory response.[102] A clinical trial showed that carbon-coated 316L SS stents substantially reduced the restenosis rate to 11%.[103] However, another clinical study showed that carbon coatings on 316L SS stents do not affect the inflammatory response.[104,105] Other studies reported restenosis of 31.8% and 35.9% for carbon-coated stents and bare metallic stents, respectively.[106] In conclusion, carbon coatings may be considered inactive because they do not improve nor deteriorate the clinical outcome.

4.2. *Polymeric coatings*

Many polymers were tried to improve the surface of 316L SS stents. Initially, the anticorrosion properties of fluorocarbon polymer coatings resulted of great interest. The main technique to coat 316L SS stents with fluorocarbon polymers is the plasma polymerization. This technique demonstrated great efficiency to produce thin, cohesive and strongly adherent coatings with the potential to inhibit corrosion by isolating the 316L alloy from the body fluids environment.[107] However, fluorocarbon polymer coatings have shown chain scission of the macromolecules, cracks of the coatings after the plastic deformation of the 316L SS substrate during stent expansion procedures, and the coatings were unable to avoid oxidation.[108] These defects were interpreted as the reasons for the observed delamination and water infiltration later derived in corrosive processes.[109] In addition, the technique requires meticulous surface preparation.[110,111]

Plasma polymerization technique was also used to coat 316L SS stents with acrylic acid, 2-hydroxyethyl methacrylate, ethylene glycol, ethylenediamine, hexamethyldisilane and hexamethyldisiloxane derived polymers.[112] However, no references were found on the performance of these coats under *in-vivo* trials.

Coatings made of polysaccharide formulations resulted with reduced cell adhesion and proliferation *in-vitro* trials.[113]

The most extensive used polysaccharide is chitosan and for stent coating application, it is used in combination with hyaluronan, another polysaccharide with anti-inflammatory properties. The preclinical results conducted in pigs of a self-assembled multilayer-coated stent showed a reduction of platelet adhesion and neointimal hyperplasia.[114] Clinical studies have not yet been reported.

The phosphorylcholine, a neutrally charged phospholipid polymer found on animal plasma membranes, has also been used as stent coating. The phosphorylcholine acts as a passive barrier to prevent SS exposure to the bloodstream or the intima of the blood vessel and has proven its hemocompatibility as its structure mimic the chemical compound found in the blood cells membrane.[115] Animal trials conducted in pigs showed that phosphorylcholine-coated stents displayed excellent biocompatibility to endothelial and blood tissues.[116] Human trials showed excellent short- and mid-term clinical outcomes with a restenosis rate of 12%.[117] However, further results showed some contradictory conclusions exposing no neointimal hyperplasia inhibition.[118] Despite no clear restenosis reduction, phosphorylcholine coating has been used as a drug eluting platform.[119]

It is worth to be mentioned that polymers have found extended applications in the manufacture of drug eluting stents.[120] Drug eluting stents constitute a separate area of vascular medicine and it is subject of many excellent review papers.[121–123] In any case, recent statistical analysis have shown that the presence of polymers may not be convenient for biocompatiblity issues at short and long periods.[124,125] This situation has initiated a vertiginous interest in the development of polymer-free drug eluting stents.[126–128]

4.3. *Organic-inorganic hybrid materials*

Silica–polyethylene glycol hybrid coatings have shown improved flexibility and excellent properties as substrate for drug release when deposited over 316L SS stents.[129]

Titanium nanoparticles coated with polyethylene glycol by plasma polymerization technique were deposited on 316L SS stents. This coating was reported with high hydrophilicity, good corrosion resistance and low protein adhesion.[130]

Despite the promising results, no *in-vivo* studies were reported.

4.4. *Porous materials*

Stents coated with microporous materials have been early tried in an attempt to promote rapid endothelialization.[131,132] Microporous polyurethane and nanoporous alumina were tried.[133–135] Microporous polymer coatings are limited by thrombus formation due to the non-flat luminal surface design, and high neointimal hyperplasia due to low pore density at the edges of the polymer coating.[136] Microporous ceramic coatings may increase the chances of restenosis by liberation of particle debris and the intrinsic presence of pores and cracks on its structure.[137]

4.5. *Biofunctional coatings*

The conceptual idea of using biocoatings is very attractive. Stents coated with endothelial cells pretended to inhibit thrombosis and neointimal hyperplasia by cell proliferation, differentiation and the release of growth factors from the stent surface.[138] However, the seeding and culture of endothelial cells on the surface of 316L SS stents is characterized by difficulties of keeping healthy cell metabolism, deleterious cell damage during the expansion process of the stent and the incapacity of keeping the cells attached to the stent surface in blood flow conditions.[139,140]

However, coatings made of smart combinations between extracellular matrices and steam cells were proposed during the last 10 years as one of the leading strategies to face the limits of stenting procedures.[141–144] But, no commercial product based on cells coatings has been market launched.

316L SS stents were also coated with biological molecules to avoid the adhesion of monocytes.[145] Coating of dopamine and hexamethylendiamine exhibited good biocompatibility and attenuated the tissue response compared with uncoated bare 316L SS stents.[146] Coatings of dihydroxyphenylalanine and l-lysine showed good anti-inflammation properties suggesting rapid reendothelialization healing process.[147] Coatings made of bivalirudin, a potent anticoagulant molecule, inhibited the platelets activation and the fibrinogen adhesion process and enhanced the adhesion of endothelial cells, the release of nitric oxide and the secretion of prostaglandin hormone. *In-vivo* trials confirmed that bivalirudin coatings inhibit the thrombus formation by the promotion of rapid, homogeneous and healthy growing of endothelial tissues on the surface of 316L SS stents.[148] Coatings made of tetraethoxysilane and methyltriethoxysilane have shown capability to control the wettability of the 316L SS stent surface and thus promoting a good substrate for the adhesion and proliferation of endothelial cells.[149]

Undoubtedly, stents coating technologies and materials demonstrated great advantages in terms of biocompatibility enhancement. However, a coating implies a strong variation of properties between the coat and the 316L SS substrate. Consequently, weak interface and delamination induced by plastic deformation during stents expansion procedure can be expected and represent the most significant disadvantage of the concept. Alternative options to coats and drugs based on the continuous variation of properties through the surface thickness are currently investigated for biocompatibility enhancement of 316L SS stents.[150]

5. Passivated Surfaces on 316L SS Stents

Besides coating, another way of enhancing corrosion resistance of stents made of 316L SS is the increasing of the thickness and/or the increasing of the chromium content in its naturally occurring protective oxide. The natural oxide layer formed on the 316L SS surface is made of a complex oxide structure of chromium, iron and nickel. The protective oxide layer shields the bulk material from the corrosive attack of several environmental factors.[151] The effectiveness of passivation on preventing corrosion of 316L SS has been extensively investigated.[152,153] In addition, excellent antitrombogenic properties of the 316L surface oxides are reported.[154]

However, if this oxide layer is broken either by chemical or electrochemical attack or by mechanical damage, localized corrosion may occur.[155] Chromium

oxide is more stable than iron oxide. In addition, nickel is the most noble element in the alloy and probably remains in its metallic state. Selective removal of the less noble metals from the first 20 Å to 50 Å of the surface eliminates oxidizing components that could become possible corrosion sites. In general, this procedure is called passivation. According to ASTM standards, passivation is defined as a controlled chemical or electrochemical treatment with a mild oxidation for the purpose of removing free iron and other foreign matter.[156] The surface concentration of chromium and nickel in 316L SS can be adjusted using several methods. Passivation can be performed by chemical,[14,157–159] electrochemical,[160] ion implantation and oxidizing gas,[161] processes.

5.1. *Chemical passivation*

In general, the chemical passivation of 316L SS is carried out by immersing the material in a nitric acid oxidizing solution. The maximization of the anticorrosion properties of the passivation process involves variations in the nitric acid concentration, temperature and time.[162,163] A typical procedure for chemical passivation of 316L SS stents is carried out by immersing the stents in a 25% (v/v) nitric acid solution during 30 min at 75°C and followed by several washings with 25% sodium carbonate aqueous solution.[8] Nitric acid passivation of 316L SS was reported to increase two to three times the thickness of the air naturally occurring oxide layer.[164] The removal of surface inclusions and the promotion of Fe_2O_3/FeOOH and Cr_2O_3/CrOOH composed protective layer by nitric acid was also proposed to explain the remarkable short-term improvement of stability of the passivated 316L SS surface.[165,166] The material resistance to static and fatigue loadings are increased and the pitting nucleation is minimized as consequence of nitric acid passivation.[67,167] Moreover, surface strains of up to 30% did not result in significant changes of the surface tension demonstrating excellent adherence and lack of cracks of the passive layer.[168]

Oxidizing sulfuric acid solutions is also reported as efficient to promote passivation of 316L SS surfaces.[169] However, for some reason, its use is not as extended as the nitric acid.

Another passivation process uses specific combinations of weak organic acids and chelates. Additionally, reducing agents, buffers, and surfactants are incorporated as formulating additives.[17] The function of the chelate molecule is to react with metal ions forming a new chemically inert specie.[170] Passivation of 316L SS using citric acid selectively dissolves and chelates iron and nickel on the surface of the alloy. As a result, an enriched chromium oxide surface with significant improvement of the corrosion resistance is obtained.[171] The chemically inert chelated metals can be removed from the oxidized surface without risk of reprecipitation.[172] The smoothness of the surface has a great influence on the efficiency of chemical passivation processes. However, chemical passivation do not alter the surface smoothness.

Platelet and protein adhesion were studied to compare the haemocompatibility of the 316L SS passivated by the nitric acid and the citric acid methods. 316L SS surfaces passivated through the citric acid method displayed better haemocompatibility than 316L SS surfaces passivated through the nitric acid method.[18] However, other authors reported little difference between the long-term performance of nitric and citric acids passivation methods when compared against natural air passivation of 316L SS.[173] Evidently, further investigation is required to define the optimal conditions for chemical passivation of 316L SS.

5.2. *Electrochemical passivation*

In general, the electrochemical passivation of 316L SS is carried out by immersing the material in an electrolytic aqueous solution and subsequent applying of a current at oxidizing potential. The maximization of the anticorrosion properties of the passivation process involves variations in the type and concentration of electrolytic salts, temperature, time and voltage.[174–176]

The composition of the electrolytic solution seems to have a crucial function on the quality of the obtained oxide layer. The presence of chloride ions in the electrolytic promotes a substantial increment of chromium in the oxide layer.[177] The mechanical stress and the metallurgical state of the 316L SS alloy have also an impact on the composition of the oxide layer. Surfaces passivated under tensile stress develop oxide layers with higher conductivity than surfaces passivated under stress-free conditions.[178]

5.3. *Ion implantation*

316 SS bare stents have been plasma coated with nitrogen and trimethylsilane.[179,180] In all cases, plasma implanted 316 SS bare stents showed improved corrosion resistance and great potential in reducing metallic ions release into the bloodstream. Plasma implantation of nitrogen was reported to impair the nickel release from nickel–titanium alloys and increase of corrosion resistance.[181–184]

Similarly, plasma implantation of carbon and oxygen resulted in a significant reduction of nickel release and corrosion susceptibility of nickel–titanium alloys.[185–187] Perfect outer chromium oxide layer of several 10s nanometers thickness and an inner layer of iron and nickel oxides could be obtained by ion implantation of 316L SS.[188] 100% chromium oxide layer could be also obtained by chemical vapor deposition of chromium followed by oxidation.[189] However, this method implies a strong variation of properties between the chromium oxide layer and the 316L SS substrate. Consequently, weak interface and delamination induced by plastic deformation during stents expansion procedure can be expected.

Ion implantation technique is also applicable to introduce passive chromium-nitrogen layers over 316L SS surface. Passive chromium–nitrogen layers demonstrated excellent performance to diminish the pinhole defect density of 316L SS surfaces.[190] Plasma deposited titanium–nitrogen and thallium–nitrogen elemental combinations were successfully implanted in 316L SS stents. Chemically stable and highly deformable passive layer were reported. However, localized corrosion was observed in both cases after 6-month immersion tests.[191]

5.4. *Gas passivation*

Air contains nearly 21% of oxygen and normal temperature and pressure is enough to allow the natural passivation of 316L SS. However, passivation can be enhanced by simple temperature increment. Fine and amorphous enriched Fe and Cr oxide layers with excellent anticorrosion properties are obtained at oxidation temperatures between 400°C and 450°C, whereas less efficient oxide crystalline layers are obtained at oxidation temperatures over 500°C.[192] In any case, results obtained using air as oxidizing gas usually presents high dispersion. Other oxidizing atmospheres are currently under exploration.

Ethylene oxide is a strong oxidizing gas commonly used for sterilization of medical materials. The exposure of 316L SS to ethylene oxide results in a beneficial slight passivation of its surface.[193] Other passivating gas is a hydrogen atmosphere at 350°C with traces of boron and lithium. Interestingly, this study reported differential elemental compositions and crystallographic structures in the obtained passive layer. The outer part of the layer was reported as $Ni_{0.75}Fe_{2.25}O_4$ inverse spinel, the intermediate part as a mixture of $Ni_{0.75}Fe_{2.25}O_4$ and Fe_3O_4 inverse spinels and finally, the inner part of the layer consists of a mixture of Cr_2O_3+ $FeCr_2O_4$ and Fe_3O_4.[194]

6. 316L SS Stents with Controlled Topography

In general, cell growth and proliferation is affected by the topography of its substrates.[195,196] In addition, the surface physical and chemical potentials can be altered modifying the surface topography.[197–199] These concepts have been proposed as an alternative to drugs, coatings and passivation for the improvement of the biological response of endothelial tissues to stent implantation.[200–202]

In previous sections, the smoothness condition of the surface was mentioned as an important factor for the performance of surface treatments and the achievement of improved corrosion and biological properties of 316L SS stents. The generation of 316L SS surfaces with topographies different than smooth or controlled roughness implies sophisticated light and electron assisted processes. Light assisted processes such as laser micromachining,[203] and microlithography,[204] and electron assisted processes such as erosive electron beam,[205] and erosive electro discharge micromachining,[206] can be mentioned as potential methods for fabrication of 316L SS stents with controlled topography. Surface textures containing uniform micro- and nano-dots, submicron-scale ripples and stripes with different periods, micron-scale ripples, stripes and composed structures and designs can be realized on 316L SS surfaces via the mentioned processing techniques. However, most of the existing knowledge is related to topographic modification of 316L SS planar surfaces. The topographic modification of complex struts designs with thickness ranging from 50 microns to 150 microns in cylindrical symmetry is a technological challenge. On the one hand,

light assisted processes may resolve the convolution from planar to cylindrical symmetries using sophisticated optical arrays. On the other hand, electron assisted processes may resolve the convolution from planar to cylindrical symmetries using precision positioning systems.

Scientific literature devoted to surface patterning of 316L SS stents is rather limited. However, few studies at the morphological, chemical, physical and *in-vitro* biological characterizations can be found. A significant enhancement of endothelialization of 316L SS stents by surface engineering using laser techniques was reported.[207] Additionally, this engineered novel surfaces resulted super-hydrophilic and low cytotoxic surface. A more recent study showed that lithographically designed surface microstructures on 316L SS stents accelerate endothelialization and decreases thrombogenicity. Compared to smooth surface, flat cubic elevations of 5 μm edge length improved endothelial cell attachment and growth under static and dynamic conditions, whereas smaller, spiky structures of 2 μm edge length had a negative influence on endothelialization. Platelet adhesion under static and flow conditions was reduced on the flat elevations and the smooth surface, as compared to the spiky structures, hollow designs and bare metal substrates.[208] Rapid endothelialization was also promoted in 316L SS stents with nano-concave features ordered in rectangular arrays and nano-pits features with different depths and diameters obtained by focused ion beam milling.[209,210] However, the metallurgical state of the 316L alloy was significantly altered by the action of the ion beam. This result may lead to the appearance of localized corrosion. Animal trials, first-in-man and statistical studies on the performance of 316L SS stents with controlled topography have not yet been reported.

7. Conclusions and Future Trends

The preferred material for stent manufacture is the 316L SS. Its global acceptance, safety and great statistical performance indicate that 316L SS will continue to be the dominant material in the manufacture of stents in the up coming years. Surface conditions of 316L SS stents can regulate cell metabolism with great influence on the clinical success of the implant. However, the interactions between the surface of 316L SS stents with blood and endothelial tissues are not yet fully understood. This lack of knowledge, is the driving force for the research of a number strategies for improving biocompatibility, reducing thrombogenicity and controlling endothelialization of 316L SS stents. Inorganic, polymeric, hybrid, porous and biofunctional coatings, chemical, electrochemical, ion implantation and gas passivation and light and electron assisted surface micro- and nano-patterning processes are under investigation in an attempt to decrease the restenosis and thrombosis rates in stenting procedures.

The future of the technique is related to the global comprehension of the implant at service conditions. It seems that the final performance of implanted 316L SS stents depends on the interrelations between geometry, material, surface, tissues and their chemical, physical and biological interactions. In this context, surface conditioning tends to be carried out avoiding or minimizing the use of other phases such as coatings and attached molecules. A clear example of this trend is the overturning of the scientific and technological interest from the early coatings technologies into electropolishing and passivating technologies and from these to light and electron assisted surface pattening.

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